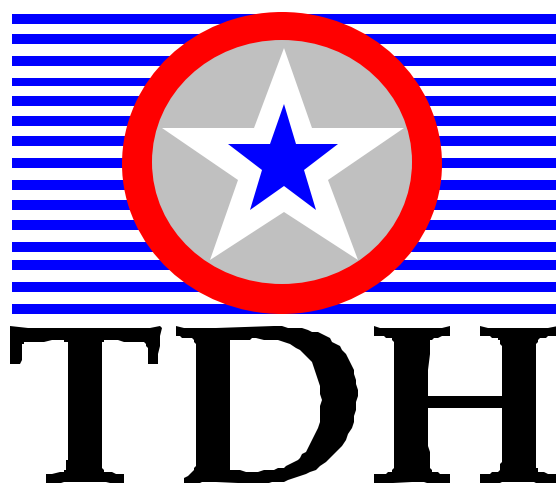


Institutional Review Board

For the Protection of Human Subjects



Instruction Packet for

**Initial/Resubmission
Protocol Review Application**

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Before You Fill In The Application

Committee Meeting Schedule, Deadlines, and Requirements Overview

Schedule. The Texas Department of Health Institutional Review Board for the Protection of Human Subjects (IRB) meets the third Thursday of each month, in Austin, beginning at 1:00 p.m.

Submission Deadline. Applications for proposal review must be submitted to the IRB by the first working day of the month. Those received after the first working day of the month that cannot be expedited will be scheduled for the following month.

Complete Application Description. A complete application consists of the Face Page, Multi-Site Collaboration information, Other IRB information, Subject Information, Additional Questions, a Synopsis of Proposal or Resubmission Summary, Consent / Assent Forms, any survey instruments (including focus group questions), letters or informational materials that will be used in the study or seen by study participants, and documentation that the human subjects research education requirements have been met.

All forms, survey instruments, letters and informational materials must be presented exactly the way that a study participant would see them. Anything less would cause the Board to defer a decision on your project, and could delay your start time.

Number of copies needed. An original and 14 copies are required with each submission.

Human Subject Protection Education: The IRB must ensure that **all** principal investigators maintain continuing knowledge of, and comply with, relevant Federal regulations, Office of Human Research Protections (OHRP) guidance, other applicable guidance, State and local law, and IRB determinations and policies for the protection of human subjects. The TDH IRB must have documentation of such training for the principal investigator as a condition for conducting human subject research. This requirement can be met by completing a web-based computer-training program (see below) or a seminar or training on human subjects protections and regulations.

One way to complete this requirement is to use the National Institutes of Health (NIH) computer-based training. The NIH has an IRB web-based training course at <http://cme.nci.nih.gov>. Complete the modules, print out completion certificate, and submit a copy of the certificate with the IRB Submission Packet.

Do You Have To Submit An Application?

Yes. Although the TDH IRB only reviews projects that meet the definition of research (see below) and are affiliated with TDH, the IRB will determine if your project meets those requirements. The following criteria are used to determine whether the TDH IRB should review a project:

Is the project research? “**Research**” means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge, 45 CFR 46.102. The TDH IRB only reviews projects that meet this definition of research.

Is the research affiliated with TDH? The TDH IRB only reviews research that is affiliated with TDH, except when the TDH IRB has been requested in writing to the Chair to serve as the IRB of a non-affiliated institution or individual, and the IRB has agreed to do so, in accordance with the provisions of 45 CFR 46. Research that is affiliated with TDH is: (i) Research sponsored or co-sponsored by TDH, (ii) Research conducted by or under the direction of any employee or agent of TDH in connection with institutional responsibilities, (iii) Research conducted by or under the direction of any employee or agent of TDH using any TDH property or facility, or (iv) Research that involves the use of TDH nonpublic information to identify or contact human research subjects or prospective subjects.

You may request your project be exempted from review or have an expedited review. What follows is the criteria the IRB will use to determine if your project can be exempted or approved by expedited review.

Exemption Criteria

Unless otherwise required by Department or Agency heads, research activities in which the only involvement of human subjects will be in one or more of the following categories are exempt from this policy. However, these exemptions do not apply to research involving prisoners, fetuses, pregnant women, or human in vitro fertilization:

(1) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

(2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless: (i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation. This exemption does not apply to research with children except for research involving observations of public behavior when the

investigator(s) do not participate in the activities being observed.

(3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section, if: (i) the human subjects are elected or appointed public officials or candidates for public office; or (ii) Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

(4) Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

(5) Research and demonstration projects which are conducted by or subject to the approval of Department or Agency heads, and which are designed to study, evaluate, or otherwise examine: (i) Public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs.

(6) Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

Expedited Review

An expedited review procedure consists of a review of research involving human subjects by the IRB Chair or by one or more experienced reviewers designated by the Chair from among members of the IRB in accordance with the requirements set forth in 45 CFR 46.110.

Research activities that (1) present no more than minimal risk to human subjects and (2) involve only procedures in one or more of the categories listed below, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110. Minor changes in previously approved research during the period (of one year or less) for which approval is authorized may also be approved by expedited review.

If you believe your project meets the qualifications for the expedited review procedure, request, in writing, that your project be reviewed by expedited review. If your project cannot be reviewed through the expedited review procedure, the project will be scheduled for full Board review at the next Board meeting based on the date you submitted the protocol

Research Categories That May Be Reviewed By the IRB Through an Expedited Review Procedure

Applicability.

Research activities that: 1) present no more than minimal risk to human subjects, and 2) involve only procedures listed in one or more of the following categories, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110. The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects. The categories in this list apply regardless of the age of subjects, except as noted.

The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal. The expedited review procedure may not be used for classified research involving human subjects.

The standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review--expedited or convened--utilized by the IRB.

Categories one (1) through seven (7) pertain to both initial and continuing IRB review.

Research Categories

(1) Clinical studies of drugs and medical devices only when condition (a) or (b) is met.

(a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)

(b) Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical

device is being used in accordance with its cleared/approved labeling.

(2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

(a) From healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or

(b) From other adults and children [children are defined in the HHS regulations as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted," 45 CFR 46.402(a). Source: 63 FR 60364-60367, November 9, 1998], considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

(3) Prospective collection of biological specimens for research purposes by noninvasive means.

Examples: (a) hair and nail clippings in a non-disfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.

(4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)

Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy

into the subject or an invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

(5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects, 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.)

(6) Collection of data from voice, video, digital, or image recordings made for research purposes.

(7) Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects, 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.)

(8) Continuing review of research previously approved by the convened IRB as follows:

(a) Where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or

(b) Where no subjects have been enrolled and no additional risks have been identified; or

(c) Where the remaining research activities are limited to data analysis.

(9) Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

Consideration Of Research Design

All American IRBs are charged with making a calculation of the balance of research risks versus the benefits. In the Common Rule, the federal regulation that governs human subjects research, IRBs are

required to determine that “risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and *the importance of the knowledge that may reasonably be expected to result*, 45 CFR 46.111(a)(2) (emphasis added).

To expand this, “[r]isks to research subjects posed by participation in research should be justified by the anticipated benefits to the subjects or society. This requirement is clearly stated in all codes of research ethics, and is central to the federal regulations,” US DHHS, Institutional Review Board Guidebook, 1993.

Thus, although IRBs are not meant to be screeners for the quality of research, it is the Board’s duty to inquire as to whether the methods used in the research are adequate to provide the benefit (i.e., the increase in knowledge) promised by the researcher. In an extreme example, a researcher could propose research that has no possibility of providing increased knowledge or other benefit. In that example, even if the risk to subjects were minimal, an IRB could not approve it under federal law.

The federal Institutional Review Board Guidebook provides a detailed chapter on considerations of research design for use by IRBs. See US DHHS, Chapter IV “Considerations of Research Design,” Institutional Review Board Guidebook, 1993. The following excerpt is taken from that chapter:

“The value of research depends upon the integrity of study results. One of the ethical justifications for research involving human subjects is the social value of advancing scientific understanding and promoting human welfare by improving health care. But if a research study is so methodologically flawed that little or no reliable information will result, it is unethical to

put subjects at risk or even to inconvenience them through participation in such a study. One question that every IRB member asks is “To what degree is it our responsibility to review the underlying science of the proposed research?” Clearly, if it is not good science, it is not ethical. The federal regulations, under which IRBs operate, however, do not clearly call for IRB review of the scientific validity of the research design. Nonetheless, they do require that IRBs determine whether “[r]isks to subjects are reasonable in relation to...the importance of the knowledge that may reasonably be expected to result” [Federal Policy §____.111(a)(2)]. If the underlying science is no good, then surely no important knowledge may reasonably be expected to result,” US DHHS, Institutional Review Board Guidebook, Chapter IV, 1993.

At the TDH IRB, the Board has always considered the scientific design of proposed studies to be well within its scope of inquiry. The Board generally does not make highly detailed inquiries into study design, but, as it is required to do, the Board does make sufficient inquiry to determine that the methods to be used have a reasonable chance of providing an answer to the scientific question being posed. In a number of cases, the Board has deferred approval of projects that failed to meet this criterion.

Researchers are now expected to have a working knowledge of human subjects research ethics. Please consult the website of the National Institutes of Health at <http://cme.nci.nih.gov>. The developments at Johns Hopkins University underscore the emphasis that the federal government places on strict adherence to human subjects protection guidelines. The TDH IRB takes its responsibility seriously in this regard.

Instructions for Completing the Initial/Resubmission Protocol Review Application

Important: If your project was previously approved by the IRB and you are submitting your project for renewal, you are using the wrong application and instructions packet. Contact the IRB Administrator for the correct materials.

Note: Italicized texts are required actions that must be completed to fill-out the application properly.

1a. Protocol Submission Type

If the IRB has not reviewed your protocol before, it is an Initial Submission. If the IRB has reviewed your protocol, required changes, and you are submitting those changes for review, it is a Resubmission.

Type an "X" to the left of the appropriate submission type.

1b. Protocol Title

The Protocol Title is the name of the study. It should be specific and brief. Being comprehensive is a secondary consideration.

Type the full name of the protocol.

2. Starting Date

The Proposed Start Date and the End Date will be estimates. The start date would be the date that recruiting participants could begin. The end date would be the point at which no human subjects are further involved.

Type the date you plan to begin the research.

3. Ending Date

See the note under Start Date.

Type the projected date you plan on completing the research.

4. Total # of Subjects

The Total # of Subjects must be the maximum number of subjects the Principal Investigator (PI) anticipates enrolling in the study. Be as precise as possible. The number needs to be supported by appropriate statistics. If the PI has to change this number after initial IRB approval, the IRB must review and approve the new number.

Type the total number of subjects you plan on recruiting for this project.

5. Principal Investigator

The Principal Investigator (PI) is the individual responsible and accountable for designing, conducting, and monitoring a protocol. The PI must be suitably qualified because the PI assumes full responsibility for the treatment and evaluation of

patients, and the integrity of the research data. The PI must assure that the protocol is followed and the data collected promptly and accurately. Specific responsibilities of a PI include, but are not limited to, writing the protocol document, assuring that necessary approvals are obtained, monitoring the protocol during its execution, analyzing the results, and promptly reporting any adverse events to the TDH IRB.

Type the name, degrees, mailing address, telephone number (including any extension), and e-mail address of the principal investigator.

6. TDH Contact

Type the name, degrees, mailing address, telephone number (including any extension), and e-mail address of the TDH employee, associated with the project, who can be contacted, if needed.

If there is no TDH Contact person, Type "NONE" on the name line.

7. Student Investigator

Type the name, title, University and department, mailing address, telephone number (including any extension), and e-mail address of your Thesis/Dissertation Chair.

If the PI is not a student, Type "NA" on the name line.

8. Project Funding Source

Type an "X" next to the appropriate funding source. If the source is Federal Agency, Thesis/Dissertation, University, or Private Company, type the additional information requested in the space provided.

9. Principal Investigator's Statement

Before signing this statement, please read the statement in the box on the application and review the PI description and responsibilities in #5 above.

The Principal Investigator must sign on the signature line; Type the date on the date line.

10. Multi-Site Collaboration

Type an "X" next to the appropriate Multi-Site Collaboration selection. If your selection was NONE, go to Other IRBs, below. Otherwise, in the Synopsis of Proposal, item i include the full name, address, telephone number, and contact person for each site.

11. Other IRBs

Review by another IRB (including the Centers for Disease Control and Prevention IRB) does not exempt a project from TDH IRB review.

List (type) all other IRBs who will review your study, including their telephone number.

12. Subject Information

Note: People from across the United States and around the world participate as research participants on protocols. The criteria the PI uses to include or exclude persons from the protocol are important because generalizable knowledge may only be obtained for that population where the research participants are a reasonable sample. If the criteria are too restrictive, the PI may not find enough participants. If the criteria are too broad, the PI may not be able to draw conclusions, because with too many people, a uniform response may not be possible. Explain in item c of the Synopsis of Proposal, your reasoning for including or excluding a class of people.

a. Characteristics

Age Groups – Select the age range(s) of the subject pool and type an “X” to the left of the appropriate age range. Check all that apply.

Fetuses – If you plan to use fetuses in your study, type an “X” to the left of the “Yes” response. Otherwise, type an “X” to the left of the “No” response.

Pregnant Women - If you plan to use pregnant women in your study, type an “X” to the left of the “Yes” response. Otherwise, type an “X” to the left of the “No” response.

Elderly/Aged - If you plan to use elderly/aged, 66+ years of age, in your study, type an “X” to the left of the “Yes” response. Otherwise, type an “X” to the left of the “No” response.

Prisoners - If you plan to use prisoners in your study, type an “X” to the left of the “Yes” response. Otherwise, type an “X” to the left of the “No” response.

Impaired - If you plan to use impaired subjects in your study, type an “X” to the left of the “Yes” response and indicate whether the subjects are physically impaired, cognitively impaired, or both by typing an “X” to the left of the appropriate response.. Otherwise, type an “X” to the left of the “No” response.

Compensation/Incentives – If you will be offering compensation or incentives to recruit study participants, type an “X” to the left of the “Yes” response and describe the compensation / incentive. Otherwise, type an “X” to the left of the “No” response.

b. Exclusions

Please reread the Note at the beginning of this section.

Type an “X” to the left of all classes of people that you will be excluding from your study. Explain in the Synopsis of Proposal item c why these classes of people are excluded.

c. Identifying Information

If you will be collecting identifying information, Type an “X” to the left of the “Yes” response and explain the reason in item c of the Synopsis of Proposal, otherwise type an “X” to the left of the “No” response and explain in item c of the Synopsis how you will exclude identifying information.

13. Additional Questions

a. Ionizing Radiation Use

Type an “X” to the left of the appropriate response.

If ionizing radiation is indicated, either medically or research, explain why in the Synopsis of Proposal, item e.

b. Investigational New Drug or Device

Type an “X” to the left of the appropriate response.

IND = Investigational New Drug. IDE = Investigational New Device. If you are testing a new drug or device, fill out (type) the following information:

FDA No.

Name (of drug or device)

Sponsor (The FDA grants IND status for chemicals or biologic agents to a “sponsor.” The sponsor must apply for IND status. The sponsor may be an individual, such as the PI, a pharmaceutical company, governmental agency, academic institution, or private organization. For administrative reasons, only one entity should be designated as the sponsor. The sponsor is approved by the FDA and is responsible for: 1) Selecting qualified investigators; 2) Giving the investigators the information they need to conduct an investigation properly; 3) Ensuring proper monitoring of the investigations; 4) Ensuring that the investigations are conducted in accordance with the general investigational plan and protocol; 5) Maintaining an IND that complies with all requirements with respect to the investigations; and 6) Ensuring that the FDA, the IRBs, and all participating investigators are informed promptly of adverse effects or risks of the drug.)

Holder (An individual, institute, or program, that is specifically designated by a sponsor to conduct a drug study is considered the “holder.” Holders report progress, adverse effects, and proposed changes to the sponsor who, in turn, reports as required to the FDA and the IRB. The sponsor and the holder can be the same entity or individual.)

a. Project Involves

This section includes 6 questions. Do not leave any responses blank. If the answer is yes, type an “X” to the left of the “Yes” response. If the answer is no, type an “X” to the left of the “No” response.

b. Submission of Non-English Translations

Our experience is that translations from English to another language using only commercial software are

not accurate enough to meet human subjects criteria for IRB approval. Someone who is fluent in the language should review all such translations for accuracy before being submitted to the IRB.

Submission of Non-English translations of consent forms and other documents should occur after the TDH IRB approval of the English version of the documents. Once approval of English version has been completed the investigator will be asked to submit 2 paper copies or an electronic copy, in Microsoft Word format, of both the English and non-English versions of the instruments being translated. TDH staff will review the non-English translations. No non-English speaking participants can be enrolled in the study until the IRB approval of the non-English documents has been granted.

14. Synopsis of Proposal or Resubmission Summary

The synopsis needs to include the following specified information as fully and yet concisely as possible. Limit your synopsis to no more than 2 pages. Every application submitted for review and approval needs to have attached to it a page organized in numerical brief paragraph form as outlined below. If the synopsis does not address every item listed below, the Board will defer a decision on your project's approval. This could delay your start date.

- a. Title of Study
- b. State the purpose of the project. Briefly, summarize the study protocol. Describe the type of study you are conducting (i.e., case control, prevalence, etc.). Describe the sample size and how the sample size was derived.
- c. Identify the sources of the potential subjects, derived materials, or data. Describe the characteristics of the subject population, such as their anticipated number, age, sex, ethnic background, and state of health. Identify the criteria for inclusion or exclusion. Explain the rationale for the use of special classes of subjects, such as fetuses, pregnant women, women of childbearing potential, children, institutionalized mentally disabled, prisoners, or others, especially those whose ability to give voluntary informed consent may be in question.
- d. Describe the procedures for recruitment of subjects and the consent procedures to be followed. Include the circumstances under which consent will be solicited and obtained, who will seek it, the nature of information to be provided to prospective subjects, and the methods of documenting consent. (Include applicable consent form(s) for review purposes.) If written consent is

not to be obtained, specifically point this out and explain why not.

- e. Describe any potential risks--physical, psychological, social, legal, or other--and assess their likelihood and seriousness. Describe alternative methods, if any, that were considered and why they will not be used.
- f. Describe the procedures for protecting against or minimizing any potential risks and include an assessment of their likely effectiveness. Where relevant, describe arrangements for providing medical treatment if needed. Include a discussion of confidentiality safeguards including the specific steps you will take to a) provide privacy during interviews, b) keep forms secure, c) keep data confidential, d) prevent release or publication of identifying data, and e) retain and ultimately dispose of records.
- g. Describe and assess the potential benefits to be gained by the subjects, and the benefits that may accrue to society in general because of the planned work.
- h. Discuss the risks in relation to the anticipated benefits to the subjects and to society.
- i. Identify the specific sites/agencies to be used as well as their IRB approval status. Include copies of IRB approval letters from agencies to be used.
- j. If you are a student, indicate the relationship of the proposal to your program of work and identify your supervising/sponsor faculty member. (In the case of student projects, pilot studies, theses, and/or dissertations, evidence of approval of Supervising Professor or Faculty Sponsor should be included. The student's committee must approve thesis and dissertation proposals before proceeding to the IRB.

Resubmission Summary

Include if the project has been reviewed by IRB and was deferred for resubmission. Summarize how the project investigators have responded to each requirement or recommendation made by the TDH IRB in the letter sent to the principal investigator after review of the project. Address each requirement separately indicating what changes and where in the application changes are documented. Please use a highlighter or other mechanism to show where changes were made in the synopsis of proposal, preliminary project questions, consent forms or other documents. Please provide a justification if no changes were made in response to a TDH IRB requirement or if an alternative solution was made to a concern raised by the IRB.

IRB Checklist

— Is your application complete? Does it include:

- Face Page
- Multi-Site Collaboration information
- Other IRB information
- Subject Information
- Additional Questions
- Synopsis of Proposal - Does your synopsis of proposal cover all aspects as outlined (Section 14)?

OR

- Resubmission Summary - Does your resubmission summary cover all aspects as outlined (Section 14)?
- Consent/Assent Forms - Do your consent/assent forms address all items on the Consent Form Checklist (page 9)?
- Any survey instruments (including focus group questions), letters or informational materials that will be used in the study or seen by study participants.

All forms, survey instruments, letters and informational materials must be presented exactly the way that a study participant would see them. Anything less would cause the Board to defer a decision on your project, and could delay your start time

- Documentation that the human subjects research education requirement has been met.
- Have you sent the required number of copies?
- One original and 14 copies. The IRB office will not make copies of submission applications; electronic or faxed submissions are **not** acceptable.
- Send the submission to:

**Texas Department of Health
Institutional Review Board
1100 West 49th Street
Austin, Texas 78756-3199**

Consent Form Checklist

- ☐ Is the language and reading level appropriate to the population?
- ☐ Does it give the title of the study and state that the study involves research?
- ☐ Does it list the agencies conducting the study?
- ☐ Does it give the purpose of the study? What the researcher hopes to learn?
- ☐ Does it state why & how the person was selected to be in the study?
- ☐ Does it state that participation is voluntary?
- ☐ Does it state that any current services or benefits received by the participant or to which they are entitled from any agency named in the form will not be affected by their decision?
- ☐ If withholding of a usual treatment of service is part of the study, is that clearly stated?
- ☐ Does it clearly state what participation will involve in terms of:
 - ☐ Time (both amount and frequency of participation)?
 - ☐ Effort?
 - ☐ Possible discomforts?
 - ☐ Risks (including risks of psychological discomforts)?
 - ☐ Any additional costs?
 - ☐ Use of placebos?
- ☐ If there is more than minimal risk, is the person told
- ☐ If and what type of medical treatment is available in case of injury?
- ☐ Where they can obtain further information? (**Note:** This must **not** be the TDH IRB).
- ☐ Does it disclose whether appropriate alternative procedures or treatments are available which may help the participant?
- ☐ Does it state that the person may withdraw from the study at any time without consequence to any of the usual benefits they receive?
- ☐ Are there statements describing how and to what extent the person's privacy and confidential information will be maintained?
- ☐ Does it include information on any incentives for subject participation and what must be done to obtain the incentive? (This should *not* be in the benefits section)
- ☐ Is the person told how they can reach (at no cost) both the investigator and an approving IRB if they have questions about the study or their rights as a participant respectively? Does it include the TDH IRB toll free number to call for questions about their rights as a research subject in addition to any other IRB phone numbers?
- ☐ Depending on the study, additional information may be necessary in the consent form.

Consent To Participate In Research Guidelines

Project Title:

IRB Number:

Principal Investigator:

INTRODUCTION

You are asked to take part in a research study conducted at [insert the study site] by [name(s) of investigator(s)] (If a student, state how the study relates to your program of work, i.e. report, thesis, dissertation). **Your participation in this study is voluntary. You should read the information below, and ask questions about anything you do not understand, before deciding whether or not to participate.**

Guidelines:

Use simple language.

Be Concise.

Use the pronoun “you” consistently throughout (except for the signature of the subject on the last page)

PURPOSE OF THIS RESEARCH STUDY

This research study is intended to [explain the purpose of the research]. I/We hope to learn [state what the study is designed to discover or establish]. You were picked to take part in this study because [state why and how the subject was selected].

PROCEDURES

If you volunteer to take part in this study, you will be asked to do the following things:

Guidelines:

- ◆ Describe the procedures chronologically using lay language, short sentences, and short paragraphs. The use of table or flow diagrams will help to organize this section and increase readability.
- ◆ Distinguish which procedures are experimental and which are standard clinical treatments. Include screening evaluations and a listing of inclusion/exclusion criteria.
- ◆ Define and explain medical and scientific terms in ordinary language (for example, describing the amount of blood to be drawn in terms of teaspoons or tablespoons).
- ◆ Specify the number of subjects expected to be enrolled, length of time for participation in each procedure, the total length of time for participation, frequency of procedures, location of the procedures to be done, etc.
- ◆ For research involving randomization of subjects, specify the randomization process.
- ◆ For research involving the use of placebo, describe “placebo” in lay terms.

POTENTIAL RISKS OR DISCOMFORTS

Guidelines:

- ◆ Identify each procedure and then describe any reasonably foreseeable risks, discomforts, inconveniences, and how these will be minimized. If unknown, state so. If applicable, state that a particular treatment or procedure may involve risks that are currently unforeseeable (to the subject, embryo or fetus, for example.) Quantify risks using understandable comparisons.
- ◆ In addition to physiological risks and discomforts, describe any psychological, social, or legal risks that might result from participating in the research. Explain the extent to which data will be kept confidential. Address local or federal reporting requirements, if any. Inform the subject about availability of follow up or referral for treatment.
- ◆ Indicate if there are special risks to women of childbearing age; if relevant, state that study may involve risks that are currently unforeseeable, e.g., to developing fetus

- ◆ If subject's participation will continue over time, state: "any new information developed during the study that may affect your willingness to continue participation will be communicated to you."

POSSIBLE BENEFITS

Guidelines:

- ◆ Describe any benefits to the subject that may be reasonably expected. If the research is not of direct benefit to the participant, explain possible benefits to others.
- ◆ If consent will be obtained from a legal representative of the subject, the direct benefit to the subject must be elaborated in the consent form.
- ◆ If there is no likelihood that participants will benefit directly from their participation in the research, state as much in clear terms. For example, "You should not expect any direct benefits for yourself from participating in this study."
- ◆ Do not include compensation or incentives in this section.

AVAILABLE TREATMENT ALTERNATIVES

Guidelines:

- ◆ Describe any appropriate alternative therapeutic, diagnostic, or preventive procedures that should be considered before the subjects decide whether or not to participate in the study. If there are no effective alternatives, state that an alternative is not to participate in the study.
- ◆ If the prospective subjects are suffering from a terminal illness, and there are no alternative treatments available, you should say so; but add that treatment of symptoms and pain control are available through supportive care. In other words, avoid suggesting that participation in the research is the only way to obtain medical care and attention.
- ◆ If prospective subjects have a chronic, progressive disorder, or which no treatment had been demonstrated to be safe and effective, say that, as well. But also describe opportunities for managing symptoms, improving ability to function, etc. so that it does not appear that the patient will be abandoned if he or she does not agree to participate.

COMPENSATION / INCENTIVES

Guidelines:

- ◆ State whether subjects will be paid or offered other benefits. If not, state so.
- ◆ If the subject will receive monies, describe the amount, when payment is scheduled, and prorated payment schedule should the subject decide to withdraw or be withdrawn by the investigator.
- ◆ If the subject will receive compensation other than money, describe it.
- ◆ If the subject will be reimbursed for expenses such as parking, bus/taxi, etc., state so.

CONFIDENTIALITY

Your identity in this study will be treated as confidential. The results of the study, including laboratory or any other data, may be published for scientific purposes but will not give your name or include any identifiable references to you. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity. If photographs, videos, or audiotape recordings of you will be used for educational purposes, your identity will be protected or disguised. **[Describe how personal identities will be shielded, disguised, etc.]**

However, any records or data obtained as a result of your participation in this study may be inspected by the sponsor, by any relevant governmental agency (e.g., Texas Department of Health), by the (your site name) Institutional Review Board, or by the persons conducting this study, (provided that such inspectors are legally obligated to protect any identifiable information from public disclosure, except where disclosure is otherwise required by law or a court of competent jurisdiction. These records will be kept private in so far as permitted by law.

Guidelines:

- ◆ Give a brief description of how personal information, research data, and related records will be coded, stored, etc. to prevent access by unauthorized personnel.
- ◆ Explain how specific consent will be requested, if any other uses are considered.

- ◆ If applicable, state if and when individual responses to survey questionnaires will be destroyed, following analyses of the data.

TERMINATION OF RESEARCH STUDY

You are free to choose whether or not to take part in this study. If you choose not to take part in this study, it will not affect your right to health care or other services to which you are otherwise entitled. You will be told of any significant new findings developed during the course of this study that may influence your willingness to continue in this study. In the event you decide to stop your involvement in the study, please notify [name, telephone no., etc.] of your decision or follow this procedure [describe], so that your participation can be properly ended.

In addition, the investigator may terminate your participation in the study without your consent under the following circumstances. [Describe] It may be necessary for the sponsor of the study to terminate the study without prior notice to, or consent of, the participants in the event that [Describe circumstances, such as loss of funding.]

AVAILABLE SOURCES OF INFORMATION

For questions about this study call:

Name:

Phone Number: [include both a local and a toll free number]

For questions you may have about your rights as a research subject call:

Principal Investigator: [Name]

Phone Number: [Telephone Number]

or

Texas Department of Health Institutional Review Board
1-888-777-5037

In case of a research-related emergency, call:

Day Emergency Number:

Night Emergency Number:

AUTHORIZATION

I have read and understand this consent form, and I volunteer to participate in this research study. I understand that I will receive a copy of this form. I voluntarily choose to participate, but I understand that my consent does not take away any legal rights in the case of negligence or other legal fault of anyone who is involved in this study. I further understand that nothing in this consent form is intended to replace any applicable Federal, state, or local laws. I also understand that I may withdraw from this study at any time without penalty.

Participant Name (Printed or Typed):

Date:

Participant Signature:

Date:

Principal Investigator Signature:

Date:

Person Obtaining Consent (Signature):

Date:

Example Consent Form (These elements must be included in any Cover Letter)

(Title of Study)

You are invited to participate in a study of (state what is being studied). My name is _____ and I am a (graduate/student/faculty/researcher) at (name of Institution/University and Department). (If a student, state how the study relates to your program of work, i.e. report, thesis, dissertation.) I/We hope to learn (state what the study is designed to discover or establish). You were selected as a possible participant in this study because (state why and how the subject was selected). If you decide to participate, you will be one of (give number of subjects being studied) subjects chosen.

If you decide to participate, I/we (or: _____ and associates) will (describe the procedures to be followed, including their purposes, how long they will take, and their frequency. Describe the risks, discomforts and inconveniences reasonably to be expected, and any benefits reasonably to be expected).

(Describe appropriate alternative procedures that might be advantageous to the subject, if any. Any standard treatment that is being withheld must be disclosed.)

Any information that is obtained in connection with this study and that can be identified with you will remain confidential and will be disclosed only with your permission. (If you will be releasing information to anyone for any reason, you must state the persons or agencies to whom the information will be furnished, the nature of the information to be furnished, and the purpose of the disclosure.)

Your decision whether or not to participate will not influence your future relations with the Texas Department of Health or (identify by name any other institution(s) and/or agency(s)). If you decide to participate, you are free to discontinue participation at any time and no harm will come to you. *

If you have questions regarding your rights as a research subject, please call the (University Institutional Review Board, phone number) or the Texas Department of Health Institutional Review Board at 1(888) 777-5037. If you have any questions regarding participation in this study, please ask us. If you have any additional questions at a later time, you may contact **(name of study investigator/coordinator, toll free phone number)**, in addition, give the address and phone number of your dissertation Chair, if appropriate). You will be offered a copy of this form to keep.

You are making a decision whether or not to participate. Your signature indicates that you have read the information provided above and have decided to participate. You may withdraw at any time after signing this form, should you choose to discontinue participation in this study. **

Signature of Participant

Date

Signature of Parent or Legal Guardian

Date

(NOTE: This line should not appear on forms that will be given to subjects consenting for themselves.)

Signature of Child

Date

(NOTE: Required when child is 7 years of age or older, or a separate Assent Form may be used, when appropriate)

Signature of Witness (when appropriate)

Date

Signature of Investigator

Date

If you are collecting your data by means of a mail-out questionnaire, you may wish to substitute the following format for these paragraphs. (All information from the Consent Form must be included in your Cover Letter as well.)

* You are under no obligation to participate in the study. Your completing and returning the questionnaire will be taken as evidence of your willingness to participate and your consent to have the information used for purposes of the study.

** You may retain the cover letter and this explanation about the nature of your participation and the handling of the information you supply.

Child's Assent Form Guidelines

Project Title:

IRB Number:

Principal Investigator:

Why am I here?

We are doing a research study. A research study is a special way to find out about something. We are trying to find out **[state the purpose of the study in simple language]**. You are here because we think you can help us, and we want to know if you want to be part of the research study.

What will happen to me?

Only if you choose to be in the study, we will ask you to [state what the child will be asked to do in simple language. Include how many times they will be asked to do something].

Will the study hurt?

We want to tell you about some things that might happen to you if you are in the study. [Describe the risks – e.g., painful procedures, other discomforts, things that take a long time].

Will I get anything for being in the study?

[Describe possible direct benefits. For example: "If you decide to be in this study, some good things might happen to you. (Description). But we don't know for sure that these things will happen. We might also find out things that will help other children some day." If there are no direct benefits, state so – "I'm sorry, but no. You will not get anything for being in the study."]

Do I have to be in the study?

You don't have to be in this study. It's up to you. If you say ok now, but want to stop later, that's ok too. All you have to do is tell us.

If I say no, will I be punished?

If you say no now, you will not be punished.

If I start, but change my mind, will I be punished?

If you say ok now, but want to stop later, you will not be punished. Just tell us.

What if I have questions?

You can ask questions at any time. Do you have any questions now? **[Answer any questions]**. If you have any questions later, please ask.

Will you tell anyone what I did in the study?

When we finish the study, we may talk to people about what the study showed us, but we will not talk about you or what you did.

I, _____, want to be in this research study.
(Print or type your name here)

(Signature of Subject, if possible)

(Age)

(Date)

(Signature of Witness)

(Date)

(Signature of Investigator)

(Date)

Example of Assent Form for Children

I agree to participate in a study about the ways children cope with strangers. I understand that this study has been explained to my mother/father/guardian and that he/she has given his/her permission for me to participate. I understand that I may decide at any time that I do not wish to continue this study and that it will be stopped if I say so. I understand that information about what I say and do will not be given to anyone else.

I understand that I will be asked questions about how I solve problems and how I feel about my family and myself. I also will be given ideas on protecting myself, that is, keeping myself safe. I also will be asked to do some drawings and I will have my picture taken. I also understand that nothing bad or wrong will happen to me if I decide to stop my participation in this study at any time.

When I sign my name to this page I am indicating that this page was read to me and that I am agreeing to take part in this study. I am indicating that I understand what I will need to do and that I may stop the study at any time.

If you have any questions about being part of this study, please ask us. If you have any additional questions at a later time, you may contact (**name of study investigator/coordinator, toll free phone number**, in addition, give the address and phone number of your dissertation Chair, if appropriate). If you have questions regarding your rights in taking part in this study, please call the (University Institutional Review Board, phone number) or the Texas Department of Health Institutional Review Board at 1(888) 777-5037.

Signature of Child

Date

Signature of Principal Investigator

Date

Example Table Of Content For IRB Submission

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The Belmont Report

Ethical Principles and Guidelines for the Protection of Human Subjects of Research

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

April 18, 1979

Ethical Principles & Guidelines for Research Involving Human Subjects

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Scientific research has produced substantial social benefits. It has also posed some troubling ethical questions. Public attention was drawn to these questions by reported abuses of human subjects in biomedical experiments, especially during the Second World War. During the Nuremberg War Crime Trials, the Nuremberg code was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This code became the prototype of many later codes intended to assure that research involving human subjects would be carried out in an ethical manner.

The codes consist of rules, some general, others specific, that guide the investigators or the reviewers of research in their work. Such rules often are inadequate to cover complex situations; at times they come into conflict, and they are frequently difficult to interpret or apply. Broader ethical principles will provide a basis on which specific rules may be formulated, criticized and interpreted. Three principles, or general prescriptive judgments, that are relevant to research involving human subjects are identified in this statement. Other principles may also be relevant.

These three are comprehensive, however, and are stated at a level of generalization that should assist scientists, subjects, reviewers and interested citizens to understand the ethical issues inherent in research involving human subjects. These principles cannot always be applied so as to resolve beyond dispute particular ethical problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects.

This statement consists of a distinction between research and practice, a discussion of the three basic ethical principles, and remarks about the application of these principles

A. Boundaries Between Practice & Research

It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research. The distinction between research and practice is blurred

partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called "experimental" when the terms "experimental" and "research" are not carefully defined.

For the most part, the term "practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals. By contrast, the term "research" designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.

When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is "experimental," in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project.

Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.

B. Basic Ethical Principles

The expression "basic ethical principles" refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethics of research involving human subjects: the principles of respect of persons, beneficence and justice.

1. Respects for Persons. -- Respect for persons

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incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.

An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so.

However, not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated.

Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them; other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequence. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations.

In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. In some situations, however, application of the principle is not obvious. The involvement of prisoners as subjects of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities for which they would not otherwise volunteer. Respect for persons would then dictate that prisoners be protected. Whether to allow prisoners to "volunteer" or to "protect" them presents a dilemma. Respecting persons, in most hard cases, is often a matter of balancing competing claims urged by the principle of respect itself.

2. Beneficence. -- Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of beneficence. The term "beneficence" is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do not harm and (2) maximize possible benefits and minimize possible harms.

The Hippocratic maxim "do no harm" has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person regardless of the benefits that might come to others. However, even avoiding harm requires learning what is harmful; and, in the process of obtaining this information, persons may be exposed to risk of harm. Further, the Hippocratic Oath requires physicians to benefit their patients "according to their best judgment." Learning what will in fact benefit may require exposing persons to risk. The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks.

The obligations of beneficence affect both individual investigators and society at large, because they extend both to particular research projects and to the entire enterprise of research. In the case of particular projects, investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to recognize the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures.

The principle of beneficence often occupies a well-defined justifying role in many areas of research involving human subjects. An example is found in research involving children. Effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research involving children -- even when individual research subjects are not direct beneficiaries. Research also makes it possible to avoid the harm that may result from the application of previously accepted routine practices that on closer investigation turn out to be dangerous. But the role of the principle of beneficence is not always so unambiguous. A difficult ethical problem remains, for example, about research that presents more than minimal risk without immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible, while others

have pointed out that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.

3. Justice. – Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of "fairness in distribution" or "what is deserved." An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. Another way of conceiving the principle of justice is that equals ought to be treated equally. However, this statement requires explication. Who is equal and who is unequal? What considerations justify departure from equal distribution? Almost all commentators allow that distinctions based on experience, age, deprivation, competence, merit and position do sometimes constitute criteria justifying differential treatment for certain purposes. It is necessary, then, to explain in what respects people should be treated equally. There are several widely accepted formulations of just ways to distribute burdens and benefits. Each formulation mentions some relevant property on the basis of which burdens and benefits should be distributed. These formulations are (1) to each person an equal share, (2) to each person according to individual need, (3) to each person according to individual effort, (4) to each person according to societal contribution, and (5) to each person according to merit.

Questions of justice have long been associated with social practices such as punishment, taxation and political representation. Until recently these questions have not generally been associated with scientific research. However, they are foreshadowed even in the earliest reflections on the ethics of research involving human subjects. For example, during the 19th and early 20th centuries the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients. Subsequently, the exploitation of unwilling prisoners as research subjects in Nazi concentration camps was condemned as a particularly flagrant injustice. In this country, in the 1940's, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population. These subjects were deprived of demonstrably effective treatment in order not to interrupt the project, long after such treatment became generally available.

Against this historical background, it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy

availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research

C. Applications

Applications of the general principles to the conduct of research leads to consideration of the following requirements: informed consent, risk/benefit assessment, and the selection of subjects of research.

1. Informed Consent. – Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied.

While the importance of informed consent is unquestioned, controversy prevails over the nature and possibility of an informed consent. Nonetheless, there is widespread agreement that the consent process can be analyzed as containing three elements: information, comprehension and voluntariness.

Information. Most codes of research establish specific items for disclosure intended to assure that subjects are given sufficient information. These items generally include: the research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Additional items have been proposed, including how subjects are selected, the person responsible for the research, etc.

However, a simple listing of items does not answer the question of what the standard should be for judging how much and what sort of information should be provided. One standard frequently invoked in medical practice, namely the information commonly provided by practitioners in the field or in the locale, is inadequate since research takes place precisely when a common understanding does not exist. Another standard, currently popular in malpractice law, requires the practitioner to reveal the information that reasonable persons would wish to know in order to make a decision regarding their care. This, too, seems insufficient since the research subject, being in essence a volunteer, may wish to know considerably more about risks gratuitously undertaken than do patients who deliver themselves into the hand of a clinician for needed care. It may be that a standard of "the reasonable volunteer" should be proposed: the extent and nature of information should be such that

persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation.

A special problem of consent arises where informing subjects of some pertinent aspect of the research is likely to impair the validity of the research. In many cases, it is sufficient to indicate to subjects that they are being invited to participate in research of which some features will not be revealed until the research is concluded. In all cases of research involving incomplete disclosure, such research is justified only if it is clear that (1) incomplete disclosure is truly necessary to accomplish the goals of the research, (2) there are no undisclosed risks to subjects that are more than minimal, and (3) there is an adequate plan for debriefing subjects, when appropriate, and for dissemination of research results to them. Information about risks should never be withheld for the purpose of eliciting the cooperation of subjects, and truthful answers should always be given to direct questions about the research. Care should be taken to distinguish cases in which disclosure would destroy or invalidate the research from cases in which disclosure would simply inconvenience the investigator.

Comprehension. The manner and context in which information is conveyed is as important as the information itself. For example, presenting information in a disorganized and rapid fashion, allowing too little time for consideration or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice.

Because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the presentation of the information to the subject's capacities. Investigators are responsible for ascertaining that the subject has comprehended the information. While there is always an obligation to ascertain that the information about risk to subjects is complete and adequately comprehended, when the risks are more serious, that obligation increases. On occasion, it may be suitable to give some oral or written tests of comprehension.

Special provision may need to be made when comprehension is severely limited -- for example, by conditions of immaturity or mental disability. Each class of subjects that one might consider as incompetent (e.g., infants and young children, mentally disable patients, the terminally ill and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving them the opportunity to choose to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored, unless the research entails providing them a

therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm.

The third parties chosen should be those who are most likely to understand the incompetent subject's situation and to act in that person's best interest. The person authorized to act on behalf of the subject should be given an opportunity to observe the research as it proceeds in order to be able to withdraw the subject from the research, if such action appears in the subject's best interest.

Voluntariness. An agreement to participate in research constitutes a valid consent only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence. Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable.

Unjustifiable pressures usually occur when persons in positions of authority or commanding influence -- especially where possible sanctions are involved -- urge a course of action for a subject. A continuum of such influencing factors exists, however, and it is impossible to state precisely where justifiable persuasion ends and undue influence begins. But undue influence would include actions such as manipulating a person's choice through the controlling influence of a close relative and threatening to withdraw health services to which an individual would otherwise be entitled.

2. Assessment of Risks and Benefits. -- The assessment of risks and benefits requires a careful arrayal of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research. Thus, the assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research. For the investigator, it is a means to examine whether the proposed research is properly designed. For a review committee, it is a method for determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate.

The Nature and Scope of Risks and Benefits. The requirement that research be justified on the basis of a favorable risk/benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained

is derived primarily from the principle of respect for persons. The term "risk" refers to a possibility that harm may occur. However, when expressions such as "small risk" or "high risk" are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and the severity (magnitude) of the envisioned harm.

The term "benefit" is used in the research context to refer to something of positive value related to health or welfare. Unlike, "risk," "benefit" is not a term that expresses probabilities. Risk is properly contrasted to probability of benefits, and benefits are properly contrasted with harms rather than risks of harm. Accordingly, so-called risk/benefit assessments are concerned with the probabilities and magnitudes of possible harm and anticipated benefits. Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm and the corresponding benefits. While the most likely types of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be overlooked.

Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society). Previous codes and Federal regulations have required that risks to subjects be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society in the form of knowledge to be gained from the research. In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight. On the other hand, interests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected. Beneficence thus requires that we protect against risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research.

The Systematic Assessment of Risks and Benefits

It is commonly said that benefits and risks must be "balanced" and shown to be "in a favorable ratio." The metaphorical character of these terms draws attention to the difficulty of making precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research, and to consider alternatives systematically. This procedure renders the assessment of research more rigorous and precise, while making communication between review board members and investigators less subject to

misinterpretation, misinformation and conflicting judgments. Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible. The method of ascertaining risks should be explicit, especially where there is no alternative to the use of such vague categories as small or slight risk. It should also be determined whether an investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.

Finally, assessment of the justifiability of research should reflect at least the following considerations: (i) Brutal or inhumane treatment of human subjects is never morally justified. (ii) Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures. (iii) When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject -- or, in some rare cases, to the manifest voluntariness of the participation). (iv) When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits. (v) Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.

3. Selection of Subjects. -- Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects.

Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients who are in their favor or select only "undesirable" persons for risky research. Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice that there is an order of preference in the selection of classes of subjects (e.g., adults before children) and that some classes of potential subjects

(e.g., the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.

Injustice may appear in the selection of subjects, even if individual subjects are selected fairly by investigators and treated fairly in the course of research. Thus injustice arises from social, racial, sexual and cultural biases institutionalized in society. Thus, even if individual researchers are treating their research subjects fairly, and even if IRBs are taking care to assure that subjects are selected fairly within a particular institution, unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research. Although individual institutions or investigators may not be able to resolve a problem that is pervasive in their social setting, they can consider distributive justice in selecting research subjects.

Some populations, especially institutionalized ones, are already burdened in many ways by their infirmities and environments. When research is proposed that involves risks and does not include a therapeutic

component, other less burdened classes of persons should be called upon first to accept these risks of research, except where the research is directly related to the specific conditions of the class involved. Also, even though public funds for research may often flow in the same directions as public funds for health care, it seems unfair that populations dependent on public health care constitute a pool of preferred research subjects if more advantaged populations are likely to be the recipients of the benefits.

One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.